

Remarks

Claims 76-90 and 92-102 are pending in the subject application. By this Amendment, claims 90 and 101 have been amended. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 76-90 and 92-102 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. §102(b) and the obviousness-type double patenting rejection over U.S. Patent No. 6,127,172.

Claims 76-78, 81, and 83-89 have been rejected as obvious over claims 14-21 of U.S. Patent No. 6,106,825 under the judicially created doctrine of "obviousness-type" double. Attached with this Amendment is a Terminal Disclaimer with respect to U.S. Patent No. 6,106,825, which obviates this rejection. Submission of the Terminal Disclaimer should not necessarily be construed as acquiescence to the "obviousness-type" double patenting rejection.

Claims 76-89 remain rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The applicants respectfully submit that the subject specification fully enables the claimed invention. The applicants have addressed each of the points raised in the Office Action in turn, in the paragraphs that follow.

The applicants gratefully acknowledge the Examiner's indication that the subject specification enables the non-therapeutic delivery of a polynucleotide encoding a protein to vertebrate cells *in vivo* using recombinant entomopoxvirus, wherein the polynucleotide is operably linked to an early poxvirus promoter.

With regard to use of a non-poxvirus promoter to express proteins *in vivo*, the Office Action indicates that, based upon the disclosed selection techniques used for expression of the DNA in cell culture, expression *in vivo* may not be detectable. Further, the Office Action indicates that the applicants' own data demonstrate that integration of the DNA is not a high percentage event in that detection of expression of the protein "requires several rounds of selection to increase the number of cells with the integrated DNA" (sentence bridging pages 5-6 of the Office Action). The applicants respectively disagree with this assertion. Rather, it is submitted that the *in vitro* assay of the

specification is a reasonable predictor of achieving detectable expression *in vivo*. The courts have established that the scope of protection must only bear "a reasonable correlation" to the scope of the claims. *E.g.*, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The applicants respectfully submit that selection of recombinants (*e.g.*, using drug resistance or luminescence detection) is merely a convenient method for confirming integration of the delivered polynucleotide within the vertebrate cell nucleus and for generating large numbers of such cells *in vitro*. However, such selection methods are not required to practice the claimed invention *in vitro* or *in vivo*. There is no requirement that the delivery and integration of the polynucleotide within the vertebrate cells occur at a particular level of efficiency. The subject specification demonstrates that delivery and integration of the polynucleotide within the nucleus of vertebrate cells does occur. All that is required is delivery and expression of the polynucleotide within the vertebrate cells, as recited by the claims. Thus, the applicants respectfully submit that whether or not the integration of the delivered polynucleotide into the vertebrate cell's nucleus is "a high percentage event" is irrelevant to the enablement of the claimed invention.

Furthermore, it is respectfully submitted that multiple selection in cell culture is not correlative with a lack of detectable expression *in vivo*. Rather, the specification indicates that cells become more resistant to G418, and become more numerous and brighter with a gradual increase in time. In fact, the subject specification indicates that "[u]ltimately, all cells in each clonal isolate were GFP-positive" (page 82, lines 14-19). Thus, it is accurate to say that such multiple rounds of selection merely provide a reliable count of transduced cells over time. Furthermore, it is submitted that the art, prior to the time of the invention, generally recognizes that *in vitro* transduction is a reasonable indicator of *in vivo* transduction. For instance, the entomopox vector of the invention comprising a non-poxvirus promoter, such as CMV or HSV-tk, functions similarly to other vector systems such as AAV which achieve nuclear integration of the DNA into the genome of a cell. For example, submitted herewith is U.S. Patent No. 5,962,313, which sets forth *in vitro* transduction with genes of interest, and subsequently demonstrates that *in vivo* transduction may be achieved at a similar efficiency with the same genes of interest (see the Examples section and Figure 9, for example). It is further respectfully submitted that the applicants are not claiming expression *in vivo*

at a particular level of efficiency, and rather are claiming expression as a result of delivery of the vector construct, such that the DNA is expressed.

The Office Action also indicates that the subject specification does not provide sufficient guidance as to dosages or routes of administration resulting in detectable amounts of protein expression *in vivo*. The applicants submit that it is not necessary to specify the dosage or administration routes where such information can be obtained by one of ordinary skill in the art without undue experimentation, as is the case here. *In re Johnson*, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 144 USPQ 637, 643 (CCPA 1965).

In view of the remarks set forth above, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 90, 92, 95, 97, and 99-102 have been rejected under 35 U.S.C. §102(e) as being anticipated by Dall *et al.* (U.S. Patent No. 5,762,924). The applicants submit that the Dall *et al.* patent does not teach or suggest the applicants' claimed invention. However, by this Amendment, in order to lend greater clarity to the claimed subject matter, the applicants have amended claim 101 to specify that the cell is a vertebrate cell. In addition, claims 90 and 101 have been amended to recite that the non-pox virus promoter sequence is activated by the cellular RNA polymerase of a vertebrate cell. Support for this amendment can be found, for example, at page 75, lines 11-24, and page 81, lines 15-24, of the subject specification. The Dall *et al.* patent describes the use of recombinant entomopoxviruses as vectors for the production of insecticidal substances. The Dall *et al.* patent indicates that the recombinant entomopoxvirus can be used for the production of desired biologically-active proteins, polypeptides, or peptides. However, the Dall *et al.* patent does not describe a recombinant entomopoxvirus containing a polynucleotide operably linked with a non-pox virus promoter sequence that is activated by the cellular RNA polymerase of a vertebrate cell. The applicants respectfully submit that there is nothing within the Dall *et al.* patent to indicate that recombinant entomopoxvirus can be utilized to deliver a polynucleotide to a vertebrate cell. As indicated at column 3, lines 40-48, of the Dall *et al.* patent, expression is preferably driven by an entomopoxvirus promoter, and only cultured insect cells, such as *Helicoverpa* or *Spodoptera*, "or similar cells" are exemplified.

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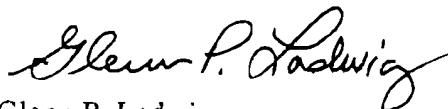
As the Examiner is aware, for a reference to anticipate under 35 U.S.C. § 102, that reference must contain, within its four corners, all of the limitations of the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991). As indicated above, the Dall *et al.* patent does not teach each and every element of the applicants' claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for a one-month Extension of Time  
Terminal Disclaimer  
Marked-Up Version of Amended Claims  
Copy of U.S. Patent No. 5,962,313

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Docket No. UF-221C1XC1

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**Marked-Up Version of Amended Claims****Claim 90 (Amended Three Times):**

A recombinant entomopoxvirus vector comprising a polynucleotide encoding a protein operably linked with a non-poxvirus promoter sequence, wherein said non-poxvirus promoter sequence is activated by the cellular RNA polymerase of a vertebrate cell.

**Claim 101 (Amended Three Times):**

A vertebrate cell comprising a recombinant entomopoxvirus vector comprising a polynucleotide encoding a protein operably linked with a non-poxvirus promoter sequence, wherein said non-poxvirus promoter sequence is activated by the cellular RNA polymerase of said vertebrate cell.